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Incidence, clinical characteristics, risk factors and outcomes of acute coronary syndrome in patients with Covid-19: Results of the UMC-19-S_{10}

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Abstract (250 words)

Background: There is a lack of knowledge about the real incidence of acute coronary syndrome (ACS) in patients with COVID-19, their clinical characteristics and prognosis.

Objective: We investigated the incidence, clinical characteristics, risk factors and outcomes of ACS in patients with COVID-19 attending the emergency department (ED).

Methods: We retrospectively reviewed all COVID-19 patients diagnosed with ACS in 62 Spanish EDs during March-April 2020 (first wave of COVID-19). We formed two control groups: COVID-19 patients without ACS (control A) and non-COVID-19 patients with ACS (control B). Unadjusted comparisons between cases and controls were performed regarding 58 characteristics and outcomes.

Results: We identified 110 ACS in 74,814 patients with COVID-19 attending the ED (1.48‰, 95%CI=1.21-1.78‰). This incidence was lower than that observed in non-COVID-19 patients (3.64‰, 95%CI=3.54-3.74‰; OR=0.40, 95%CI=0.33-0.49). The clinical characteristics of COVID-19 patients associated with a higher risk of presenting ACS were: previous coronary artery disease, age ≥60 years, hypertension, chest pain, raised troponin, and hypoxemia. Need for hospitalisation and admission to intensive care and in-hospital mortality were higher in cases than in control group A (adjusted OR [aOR] 6.36 [95%CI=1.84-22.1], aOR 4.63 [95%CI=1.88-11.4], aOR 2.46 [95%CI=1.15-5.25]). When comparing cases with control group B, the aOR of admission to intensive care was 0.41 (95%CI=0.21-0.80), while the aOR for in-hospital mortality was 5.94 (2.84-12.4).

Conclusions: The incidence of ACS in COVID-19 patients attending the ED was low, around 1.48‰, but could be increased in some circumstances. COVID-19 patients with ACS had a worse prognosis **than controls** with higher in-hospital mortality.

Key words: acute coronary syndrome, COVID-19, SARS-Cov-2, incidence, clinical characteristics, risk factors, outcome

Introduction

Coronavirus 2019 (COVID-19) is a novel disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In March 2020, the World Health Organization declared COVID-19 a pandemic, **with more than 228 million confirmed cases of COVID-19 and 4,697,099 deaths being declared on September, 2020[1].**

Symptomatic patients with COVID-19 mainly present with fever and respiratory symptoms, with dyspnoea and lung infiltrates being present in more than 50% of hospitalised cases[2]. However, a significant number of other features can also be present, and there is growing concern about cardiovascular system involvement. COVID-19 has been related to acute coronary syndrome (ACS), acute myocardial injury, myocarditis, stress cardiomyopathy and arrhythmias[2-4]. COVID-19 causes a pro-inflammatory and prothrombotic state, which can trigger ACS[5]. Furthermore, an association has been reported between the severity of COVID-19 infection and several heart conditions such as coronary artery disease, hypertension, and diabetes[6-7]. On the other hand, some studies have found a decline in hospitalisation rates for ACS, and admissions for most diagnoses decreased by approximately 50% in the first wave of the COVID-19 pandemic between March and April 2020[8-9]. In this scenario, there is a lack of knowledge about the real incidence of ACS in patients with COVID-19, their clinical characteristics and prognosis.

Taking into account all these gaps, we designed the current study with the following specific objectives: 1) to determine the frequency of ACS in patients with COVID-19; 2) to describe whether there is any distinctive clinical characteristic in these patients in comparison with COVID-19 patients without ACS and ACS patients without ACS; and 3) to investigate the outcomes of COVID-19 patients presenting ACS.

Methods

Study design and setting

The present study forms part of the Unusual Manifestations of COVID-19 (UMC-19) project, which was designed to investigate the potential relationships between COVID-19 and 10 different entities that could be influenced by SARS-Cov-2 infection itself because of the publication of at least one case with such manifestations at the time of project design, suggesting a potential link with this viral infection. The main objectives of the UMC-19 project were common for all entities, and consisted in the description of the incidence, clinical characteristics, risk factors and outcomes for each particular entity (cases), using as comparators COVID-19 patients that did not develop this entity (control group A) as well as non-COVID-19 patients that presented this entity (control group B). Complete details of the UMC-19 project have been published elsewhere[10-11].

In Spain, the first case of SARS-Cov-2 infection was detected on January 31st, 2020 and, accordingly, the definition of the COVID-19 period for patient inclusion in the present study was set from March 1st to April 30th, 2020. During this 61-day period, 213,435 cases of COVID-19 were confirmed by the Spanish Ministry of Health[12]. For the recruitment of non-COVID controls, the UMC-19 project selected patients from two different periods: one corresponding to the same dates as the cases (from March 1st to April 30th, 2020) and the other corresponding to the same period of the previous year (from March 1st to April 30th, 2019).

The investigators of the UMC-19 project initially contacted 152 Spanish emergency departments (EDs), which roughly constitute half of the 312 hospital EDs of the Spanish public health network. Of these, 81 were willing to participate and analysed the protocol, and finally 62 consented to participate and duly sent all the required data (**Figure 1**). Altogether these 62 hospitals provide health coverage to 15.1 million citizens (32% of the population of 46.9 million of Spain) and make up a balanced representation of the Spanish territory (representing 12 of the 17 Spanish autonomous communities), type of hospital (community, reference and high technology university hospitals were included) and involvement in the pandemic (with EDs attending from 1% to 47% of the ED census corresponding to COVID-19 patients during the COVID-19 outbreak period).

The investigation of ACS in COVID-19 patients, one of the entities included in the UMC-19 project, was labelled the UMC-19 Study 10 (UMC-19-S_{10}) and consisted of a retrospective, case-control, ED-based, multicentre study that reviewed the medical reports of COVID-19 patients diagnosed with ACS during ED assessment and managed in Spanish EDs before hospitalisation.

Cases and controls of the UMC-19-S10

The case group was formed by COVID-19 patients diagnosed with ACS at ED presentation based on the medical records and their review by the principal investigator of each centre without external review. ACS included patients with suspicion or confirmation of acute myocardial ischemia or infarction (myocardial infarction and unstable angina). The definition of myocardial infarction was according to the 4th Universal Definition of Myocardial Infarction[13] .Diagnosis of COVID-19 was accepted on the basis of SARS-Cov-2 antigen detection in nasopharyngeal swab by reverse transcriptase polymerase chain reaction (RT-PCR) and a clinically compatible clinical picture (including at least malaise, fever and cough) or the presence of typical lung parenchymal infiltrates in chest X-ray (bilateral interstitial lung infiltrates and ground-glass infiltrates) in patients with some clinical symptoms attributable to COVID-19.

We defined two different control groups. One group was made up of COVID-19 patients without ACS attending the ED during the same period of the COVID-19 outbreak (March 1st to April 30th, 2020), hereafter referred to as the non-ACS-COVID-19 or control group A. This group was formed by selecting 3 COVID-19 patients for every case detected by each centre. Selection was performed randomly from the full list of patients with this final diagnosis after complete patient assessment in the ED and by cardiologists. Control group A was specifically designed to uncover the risk factors for ACS development in COVID-19 patients. The second control group was made up of all non-COVID-19 patients with a diagnosis of ACS attending the ED during the same period as the cases (March 1st to April 30th, 2020) and was defined in the same terms as the cases. In order to avoid the possibility that some of these control cases could eventually have inadvertent infection by SARS-Cov-2, in this group we also included all patients with ACS diagnosed in the ED from March 1st to April 30th, 2019, just one year before the COVID-19 pandemic. This group is hereafter named the ACS-non-COVID-19 or control

group B. Control group B was specifically designed to uncover the specific distinctive clinical characteristics of ACS developed in COVID-19 patients with respect to ACS developed in the general population. For patients with ACS, we also recorded the diagnostic tests used for diagnosis and the final classification as type-I myocardial infarction, type-II myocardial infarction or angina pectoris.

Case and control definitions are summarized in Table 1 supplementary material.

Independent variables

We collected 36 independent variables, which included 2 demographic data (age, sex), 12 comorbidities (chronic obstructive pulmonary disease, asthma, active smoker, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, obesity -clinically estimated-, cerebrovascular disease, chronic kidney disease –creatinine >2 mg/dL-, dementia, active cancer), 16 signs and symptoms recorded at ED arrival (time elapsed from symptom onset to ED attendance, fever, cough, dyspnoea, chest pain, syncope, abdominal pain, vomiting, diarrhoea, confusion, headache, anosmia or dysgeusia, temperature, systolic blood pressure, heart rate, hypoxemia –pulsioximetry <96%-, 6 laboratory parameters (cardiac troponin, C-reactive protein –CRP-, creatinine, haemoglobin, lymphocytes, D-dimer)

Outcomes

We defined 4 different outcomes for cases and controls: 1) the need for hospitalisation; 2) the need for admission to the intensive care unit (ICU); 3) in-hospital mortality; and 4) diagnostic tests (electrocardiogram, echocardiogram, , coronary stress test, coronary scan, invasive cardiac catheterization) performed in COVID-19 patients with ACS and non-COVID-19 patients with ACS.

Statistical analysis

Discrete variables were expressed as absolute values and percentages, and continuous variables as mean and standard deviation (SD). Frequencies were expressed per thousand (‰) cases or controls, with a 95% confidence interval (CI). The relative frequency of ACS was expressed per thousand (‰) of

COVID-19 or non-COVID-19 patients coming to the ED, and the incidence was expressed per 100,000 COVID-19 or non-COVID-19 individuals per year. To estimate the COVID-19 and non-COVID-19 population in each ED catchment area, we used the seroprevalence of SARS-CoV-2 in the province where the ED was located. These detailed seroprevalences were determined in a wide Spanish study performed from April 27th to May 11th, 2020[14]. Estimations of relative frequencies and annual incidences were made with 95% CI calculated using the exact method for binomial distributions.

Differences between the case and the control groups were assessed by the chi-square test (or Fisher exact test if needed) for qualitative variables, and the Student's t test for quantitative variables. The magnitude of associations was expressed as unadjusted odds ratio (OR) with 95% CI, using logistic regression, with previous dichotomization of the statistically significant continuous variables using clinically meaningful cut-offs. For calculations of adjusted OR (aOR), missing values in the independent variables were replaced using the multiple imputation technique provided by SPSS software, generating five datasets in which there are no misses among all the variables included in the adjustment.

Statistical significance was accepted in all comparisons if the p value was < 0.05 or if the 95% CI of the risk estimations excluded the value 1. The analyses were performed with the SPSS (v.24) statistical software package (IBM, Armonk, New York, USA).

Ethics

The UMC-19 project was approved by the Ethics Committee of the XX (Spain)(which acted as the central ethical committee) with reference number HCB/2020/0534.

Results

A total of 74,814 patients with COVID-19 were attended in the 62 Spanish EDs participating in the UMC-19-S6 (**Figure 1**) during the 61-day study period. One hundred ten of these patients presented ACS (frequency=1.48‰, 95%CI=1.21-1.78‰) and constituted the case group. Control group A was formed by 330 randomly selected COVID-19 patients without ACS during the same period**.** COVID-19 infection was confirmed by positive RT-PCR results in nasopharyngeal swab in 89 cases (80.9%) and

242 control A patients (73.3%) (p=0.11). On the other hand, 1,388,879 non-COVID-19 patients were seen during the 122-day period (962,726 during the 61 days in the 2020 COVID-19 period, and 423,153 during the 61 days in the 2019 pre-COVID-19 period), and 5,052 diagnoses of ACS were made in non-COVID patients (frequency=3.64‰, 95%CI=3.54-3.74), 3,388 in 2019 and 1,664 in 2020. These patients constituted control group B.

We found a significantly lower prevalence of ACS in the COVID-19 group as compared to the non-COVID group (1.48% vs. 3.64%; OR 0.40, 95% CI =0.33-0.49). On the other hand, the overall annual standardized incidences of ACS were 92.7 per 100,000 COVID individuals and year (95%CI=85.8-100.0) and 102.8 per 100,000 non-COVID individuals and year (95%CI=101.2-104.5; with partial standardized annual incidences of 69.8 in the 2020 COVID period and 134.7 in the 2019 pre-COVID period). Accordingly, the OR for the standardized annual incidence of ACS in COVID compared to non-COVID patients was 0.90 (95%CI=0.83-0.97) (OR compared to 2020 COVID period of 1.33, 95%CI=1.23-1.44; OR compared to 2019 pre-COVID period of 0.69, 95%CI=0.64-0.74). Otherwise, the OR for the standardized annual incidence of ACS in non-COVID patients during 2020 respect to 2019 was 0.52 (95%CI=0.51-0.53).

The mean age of COVID-19 patients with ACS (cases) was 74 years, 70% were males, and the most frequent comorbidities were hypertension (78%), dyslipidemia (55%), previous coronary artery disease (42%) and diabetes mellitus (30%). The remaining baseline characteristics are shown in **Table 1.** The most frequent symptomatology was dyspnoea (66%), chest pain (62%), fever (41%) and cough (38%). However, it should be highlighted that 41 (37%) patients did not have chest pain. The median time from first symptom onset to ED consultation was 3 days. The remaining clinical characteristics, as well as the vitals at ED arrival and the laboratory findings are presented in **Table 2**.

When cases were compared with controls, some statistically significant differences were found. In summary, cases compared to control group A (non-ACS-COVID-19) were older, predominantly male, and had a higher frequency of cardiovascular risk factors (smoking, hypertension, diabetes, dyslipemia), prior coronary disease and chronic renal failure. Regarding the clinical, findings at ED arrival, the symptoms of the cases were shorter lasting, and they less frequently had fever, cough and

dyspnoea, anosmia or dysgeusia but more frequently presented chest pain, hypotension and hypoxemia. Regarding the laboratory findings, cases more frequently had raised troponin, creatinine and D-dimer but lower haemoglobin values (**Table 2**). On the other hand, cases compared to B controls (ACS-non-COVID-19) were older, with a lower frequency of active smokers and a higher frequency of hypertension, coronary artery disease and cerebrovascular disease. Regarding the clinical findings at ED arrival, the cases had longer lasting symptoms, a higher frequency of respiratory symptoms, diarrhoea, confusion, headache, and a lower frequency of chest pain, and more frequently had fever and hypoxemia (**Table 2**). Some of these statistically significant differences remained in the adjusted analysis (**Table 3)**. When cases were compared with control group A, the risk factors of ACS were previous coronary artery disease, age ≥ 60 years, hypertension, chest pain, raised troponin, hypoxemia; and patients with symptoms lasting less than 3 days had lower risk. On comparing cases with control group B, the risk factors of presenting ACS were fever, diarrhoea, cough, dyspnoea and lymphopenia.

Regarding the diagnostic tests for ACS (**Figure 2**), the cases less frequently underwent echocardiography and invasive coronary angiography compared to control group B patientsCoronariography using computerized tomography and stress tests were seldom performed (1.2% and 1.9%, respectively), with no differences between the two groups. The final diagnosis of ACS included a significantly lower proportion of type-1 myocardial infarction and a higher proportion of type-II myocardial infarction in COVID-19 patients, while the proportion of angina at diagnosis was very similar (Figure 2).

COVID-19 patients with ACS were hospitalised in 95.5% of cases; 21.8% were admitted to intensive care at some point during hospital stay, and 39.1% died during hospitalisation. All the outcomes measured were worse in the cases than in control group A (**Figure 3**). Specifically, COVID-19 patients with ACS had an aOR for need for hospitalisation of 6.36 (95%CI=1.84-22.1), an aOR for need for admission to the ICU of 4.63 (95%CI=1.88-11.4) and an aOR for in-hospital mortality of 2.46 (95%CI=1.15-5.25). On the other hand, when comparing cases with control group B the aOR for admission to the ICU was 0.41 (95%CI=0.21-0.80), while the aOR for in-hospital mortality was 5.94 (95%CI=2.84-12.4).

Discussion

The first relevant finding of UMC-19-S_{10} is that the frequency of ACS in patients with COVID-19 coming to the ED was lower than that of ACS in non-COVID-19 patients, with an OR of 0.40. Even taking into account that non-COVID patients less frequently visited the ED than in previous years (the OR for 2019 respect to 2020 was 0.51, in line with previous literature [15,16], the extrapolation of these frequencies to standardized annual incidences showed that ACS in COVID-19 compared to non-COVID-19 patients was not increased either (OR=0.90). This finding contradicts previous studies that demonstrated an increased incidence of ACS in COVID-19 patients[17] and may be explained by different reasons. One explanation is that the relationship between ACS and COVID-19 had not been described at the time of inclusion. Up to 30% of patients with ACS may have had no signs of typical symptomatology[18] and, therefore, an active search for the diagnosis of ACS was not performed in those patients who already had COVID-19. In this sense, some authors advocate for cardiac troponin determination in COVID-19 patients, not only for diagnosing ACS but also for risk stratification[19]. It should be noted that cardiac troponin elevation is a common finding in about 10 to 30% of hospitalised COVID-19 patients, and most patients with troponin elevation and COVID-19 do not have a clinical presentation suggestive of ACS and are labelled as acute myocardial injury and not ACS[20]. Furthermore, during the inclusion period, there was a lack of diagnostic tests in Spain[21], and it is therefore possible that patients with ACS, but COVID-19 paucisymptomatic, with scarce respiratory symptoms or absence of fever were not tested and were considered as non-COVID-19 patients. Additionally, several studies have found that the incidence of hospitalisation for acute myocardial infarction and admissions decreased during the pandemic[8,9,22], which might be explained by patient fear of being infected if hospitalised and healthcare redistribution.

The second relevant finding was that we identified clinical characteristics that identify patients with COVID-19 with a higher risk of ACS, such as previous coronary artery disease, age > 60

years, and hypertension. These risk factors have been previously described[4,6] and could be used as a red flag to identify patients who would benefit from a targeted cardiac evaluation. On the other hand, we also identified some clinical characteristics, such as diarrhoea, cough, dyspnoea, or lymphopenia that could warn of possible COVID-19 infection in an ACS patient. However, in the current context of mandatory COVID-19 testing in all patients admitted to hospital[23, 24] this finding is of minor relevance.

Third, we found some relevant differences in patient outcomes. The smaller number of echocardiographies and coronariographies performed in COVID-19 patients with ACS could be a direct consequence of the pandemic. Deferring echocardiography studies deemed non-urgent has reduced patient?? volumes and should be understood as an effort to protect patients and echocardiography laboratory staff members[25]. The important reduction in the activity of interventional cardiology has been previously described in Spain during the first wave of COVID-19 and was due to different factors[26].

COVID-19 infection involves a higher risk for myocardial oxygen supply-demand mismatch (type 2 myocardial infarction) due to responses to acute infection, including the release of inflammatory factors and catecholamines, as well as the consequences of hypoxia, and haemodynamic instability[20]. Regarding prognosis, not surprisingly, COVID-19 patients with ACS had a worse prognosis in terms of need for hospitalisation, need for admission to the ICU and in-hospital mortality than COVID-19 patients without ACS. On the other hand, COVID-19 patients with ACS had a lower need for ICU admission with higher in-hospital mortality than ACS without COVID-19. Several reasons may explain this result. There was a higher incidence of type 2 acute myocardial infarction in patients with COVID-19, and these patients have a different profile, older age and high comorbidity[27] which could have conditioned their admission to the ICU[28]. Moreover, in the context of ICU saturation in the first wave of the pandemic, it is possible that some patients spent the first 24 hours of monitoring in the ED with subsequent transfer to a conventional hospital ward. This result coincides with a recent study conducted in 7 Spanish hospitals in which COVID-19 infection was an independent predictor of in-hospital mortality in patients with acute myocardial infarction[29].

Limitations

This study has several limitations. First, ACS was only detected if the diagnosis was performed in the ED, and ACS developing during the hospitalisation of COVID-19 patients was not taken into account. Second, in some cases, especially critical ill patients, type 2 myocardial infarction can be difficult to distinguish from acute myocardial injury. To minimize this possible misclassification, all the investigators reviewed the cases based on the 4th Universal Definition of Myocardial Infarction criteria. Third, in about one in four of the COVID-19 patients, diagnosis was based on clinical and/or radiological findings, with no microbiological confirmation, and these figures were similar to those in most countries during the first wave of the pandemic due to the shortage of tests. Fourth, as a retrospective study, although the case record form was standardized, there was no monitoring of data collection methods. In addition, outcome adjudication was performed at each hospital level, without external validation. Nonetheless, the outcomes assessed in the present study were very objective (hospitalisation, ICU admission, death), and probably no error was committed in this step. Fifth, although the UMC-19-S_{10} involved 62 EDs, it was carried out in a single country and external validation in other countries is needed before our findings can be generalised. Sixth, as treatments provided during hospitalisation were not recorded, the impact of inappropriate management on outcomes**,** especially in-hospital mortality, was not assessed in the present study. **Seventh, the administration of anticoagulation treatment decreased adverse events in COVID-19 patients. However, at the time of the study this treatment was not routinely administered as there was no evidence on this point at the time the study was performed.**

Conclusions

Despite the above limitations, we conclude that the incidence of ACS in COVID-19 patients attending the ED is low, about 1.48‰. In some circumstances, especially in COVID-19 patients with previous coronary artery disease, age ≥ 60 years, hypertension, chest pain, raised troponin, hypoxemia, and symptoms lasting less than 3 days, this incidence could be increased. COVID-19 patients with ACS had a worse prognosis than **control groups** as well as a higher in-hospital mortality.

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Article summary

1. Why is this topic important?

There is a lack of knowledge about ACS in patients with COVID-19.

2. What does this study attempt to show?

We investigated the incidence, clinical characteristics, risk factors and outcomes of acute coronary syndrome (ACS) in patients with COVID-19 attending the emergency department (ED).

3. What are the key findings?

The incidence of ACS in COVID-19 patients attending the ED is low, at around 1.48‰. This incidence could be increased in some circumstances, especially in COVID-19 patients with previous coronary artery disease, age ≥60 years, hypertension, chest pain, raised troponin, hypoxemia, and symptoms lasting <3 days. COVID-19 patients with ACS had a worse prognosis than the control groups as well as a higher in-hospital mortality.

4. How is patient care impacted?

The association of COVID-19 with ACS should be taken into consideration in decision making.

Figure 1: Study design and patient inclusion flow chart.

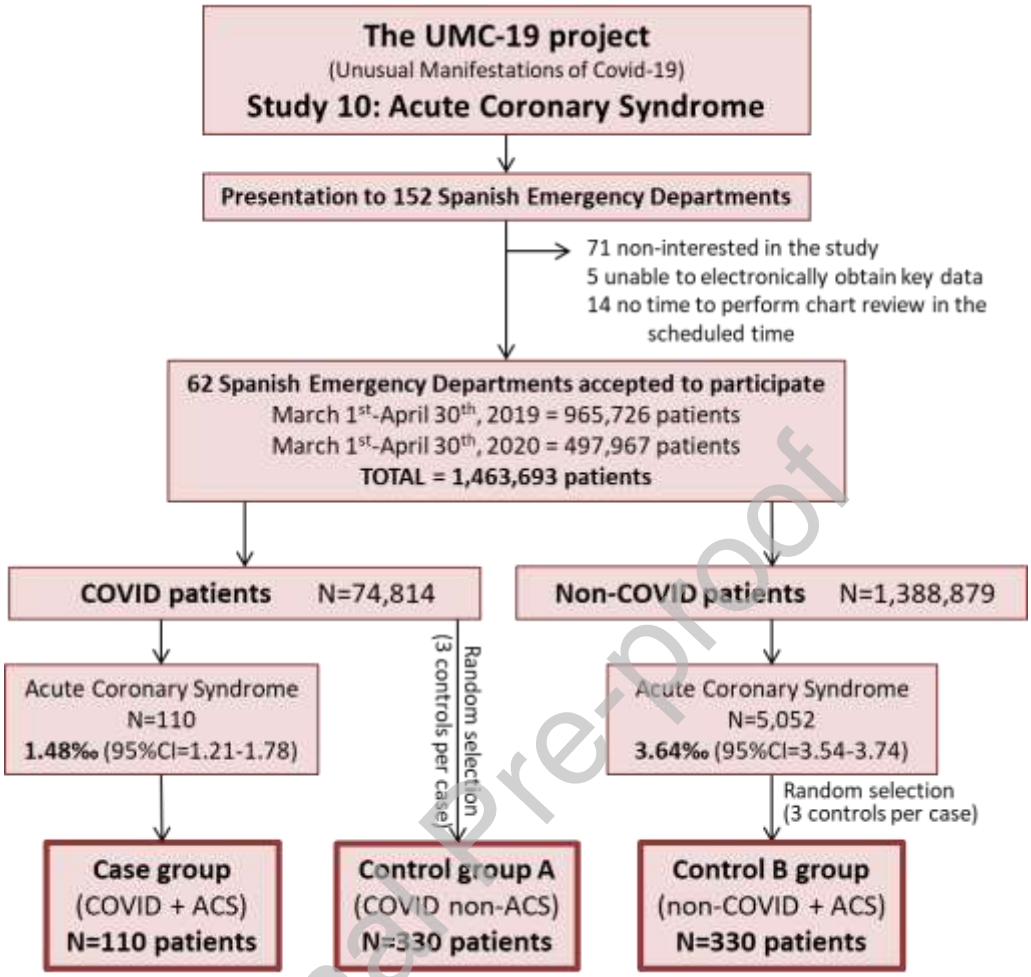
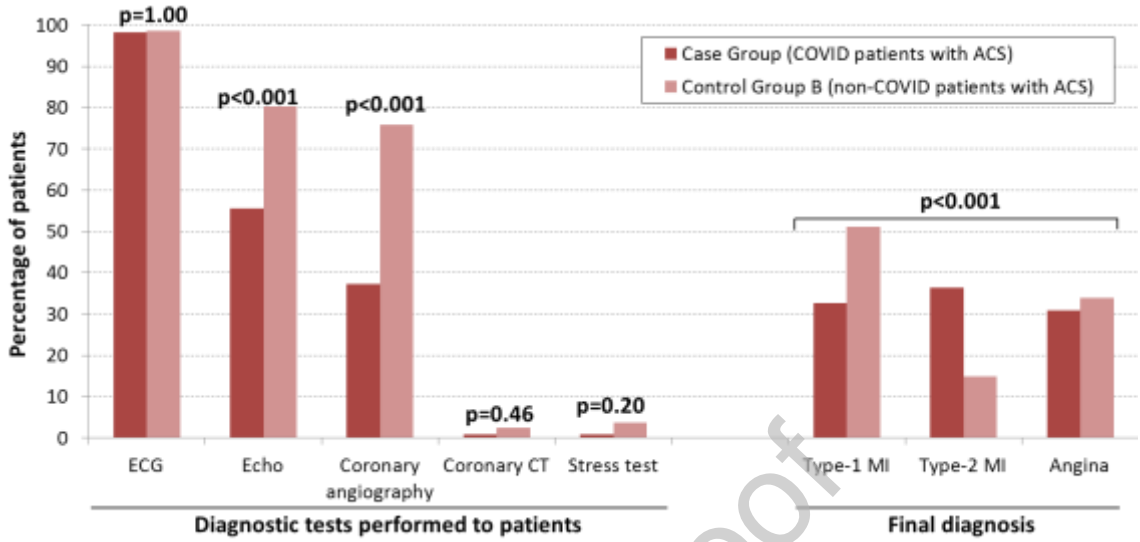
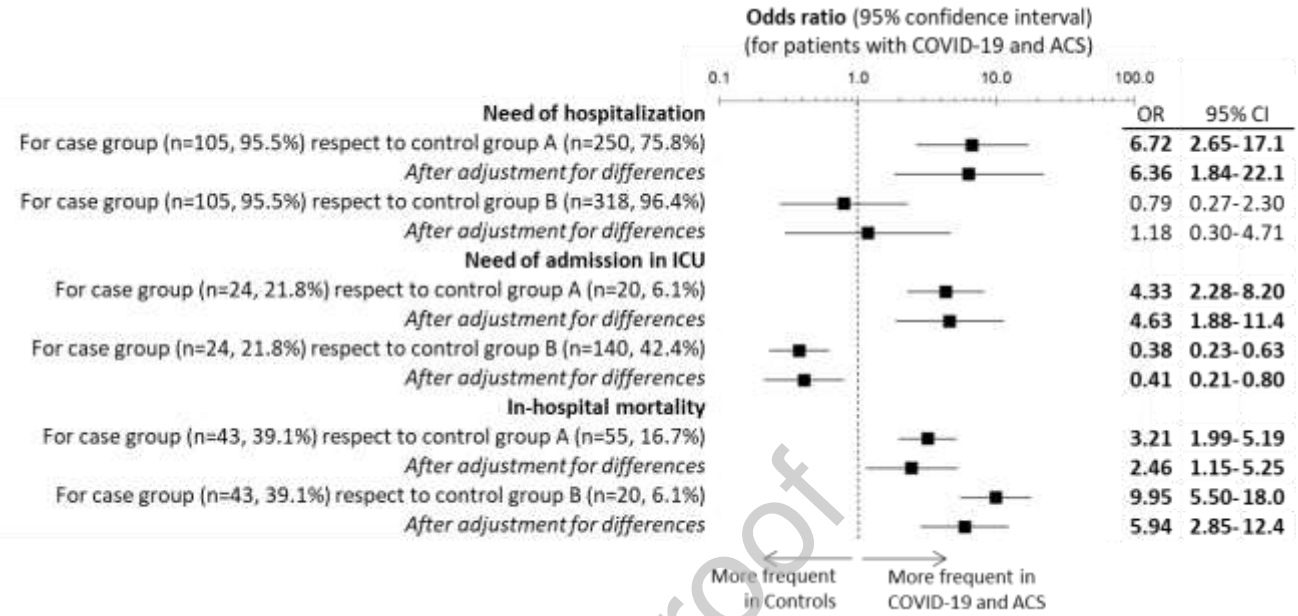


Figure 2: Diagnostic tests for acute coronary syndrome and final diagnosis.



ACS: acute coronary syndrome; Echo: echocardiography

Figure 3: Outcomes of patients with COVID-19 and acute coronary syndrome compared with controls.



Cases were COVID-19 patients diagnosed with ACS at ED presentation. Control A: COVID-19 patients without ACS attending the ED during the same period (March 1st to April 30th, 2020). Control B: Non-COVID-19 patients with a diagnosis of ACS during the same period (March 1st to April 30th, 2020) and also for the same period of the previous year (March 1st to April 30th, 2019).

Numbers denote statistical significance (p<0.05)

The multivariate analysis was adjusted for all significant variables.

Table 1: Baseline characteristics of patients with COVID-19 with acute coronary syndrome and comparison with patients with COVID-19 without acute coronary syndrome (control group A) and with patients without COVID-19 with acute coronary syndrome (control group B).

	Cases (COVID-19 and ACS) n=110	**Control group A (COVID-19 and non- ACS) N=330**	**Control group B (non-COVID-19 and ACS) N=330**	**P value[1]**	**P value[2]**
Demographics					
Age (years) [mean (SD)]	74 (13)	63 (18)	67 (14)	**<0.001**	**<0.001**
Age ≥60 years	95 (86.4)	196 (59.4)	231 (70.0)	**<0.001**	**0.001**
Sex (female)	33 (30.00%)	156 (47.27%)	98 (29.70%)	**0.002**	0.95
Pulmonary comorbidities					
Chronic obstructive pulmonary disease	15 (13.64%)	28 (8.48%)	40 (12.12%)	0.12	0.68
Asthma	4 (3.64%)	23 (6.97%)	10 (3.03%)	0.21	0.75
Active smoker	11 (10.00%)	22 (6.67%)	80 (24.61%)	**<0.001**	**0.002**
Other comorbidities					
Hypertension	86 (78.18%)	150 (45.45%)	212 (24.24%)	**<0.001**	**0.007**
Dyslipidemia	61 (55.45%)	110 (33.33%)	166 (50.30%)	**<0.001**	*0.35*
Diabetes mellitus	33 (30%)	57 (17.27%)	108 (32.73%)	**0.004**	0.57
Coronary artery disease	47 (42.73%)	25 (7.58%)	92 (27.88%)	**<0.001**	**0.004**
Obesity (clinically estimated)	19 (17.27%)	51 (15.45%)	74 (22.42%)	0.65	0.25
Cerebrovascular disease	14 (12.73%)	23 (6.97%)	19 (5.79%)	0.06	**0.016**
Chronic kidney disease	17 (15.45%)	21 (6.36%)	38 (11.52%)	**0.003**	0.28
Dementia	10 (9.09%)	29 (8.79%)	17 (5.15%)	0.92	0.14
Active cancer	13 (11.82%)	31 (9.39%)	46 (13.94%)	0.46	0.57

[1] *P values refer to comparison between cases and control group A*

[2] *P values refer to comparison between cases and control group B*

ACS: acute coronary syndrome

Table 2: Clinical, analytical and radiological characteristics of the acute episode in patients with acute coronary syndrome and comparison with patients with COVID-19 without acute coronary syndrome (control group A) and with patients without COVID-19 with acute coronary syndrome (control group B).

	Cases (COVID-19 and ACS) n=110	**Control group A (COVID-19 and non- ACS) N=330**	**Control group B (non-COVID-19 and ACS) N=330**	**P value[1]**	**P value[2]**
Symptoms at ED arrival					
Duration of symptoms (days) [median (IQR)]	3 (1-7)	7 (3-10)	1 (0-3)	**<0.001**	**<0.001**
Lasting ≥3 days	47 (42.7)	243 (73.6)	57 (17.3)	**<0.001**	**<0.001**
Fever	46 (41.82%)	193 (58.48%)	4 (1.21%)	**0.002**	**<0.001**
Cough	42 (38.18%)	191 (57.88%)	9 (2.73%)	**<0.001**	**<0.001**
Dyspnoea	73 (66.36%)	182 (55.15%)	88 (26.67%)	**0.039**	**<0.001**
Chest pain	69 (62.73%)	42 (12.73%)	285 (86.36%)	**<0.001**	**<0.001**
Syncope	8 (7.27%)	14 (4.24%)	21 (6.36%)	0.21	0.74
Abdominal pain	7 (6.36%)	17 (5.15%)	19 (5.76%)	0.63	0.82
Vomiting	8 (7.27%)	24 (7.27%)	31 (9.39%)	1	0.49
Diarrhoea	13 (11.82%)	54 (16.36%)	5 (1.52%)	0.25	**<0.001**
Confusion	11 (10.00%)	25 (7.58%)	13 (3.94%)	0.42	**0.015**
Headache	8 (7.27%)	39 (11.82%)	4 (1.21%)	0.18	**0.001**
Anosmia or dysgeusia	3 (2.7)	32 (9.7)	2 (0.6)	**0.02**	0.07
Signs at ED arrival					
Fever (>37.3ºC)	29 (26.6)	76 (23.5)	4 (1.2)	0.52	**<0.001**
Hypotension (<90 mmHg)	6 (5.5)	7 (2.2)	12 (3.6)	**0.08**	0.40
Tachycardia (>100 bpm)	18 (16.4)	72 (22.3)	44 (13.4)	0.19	0.44
Hypoxemia (pulsioxymetry <96%)	65 (59.6)	148 (45.5)	94 (28.5)	**0.01**	**<0.001**
Laboratory findings [mean (SD)]					
Raised troponin (>99th percentile)	90 (85.7)	28 (24.1)	274 (86.4)	**<0.001**	0.85
Creatinine > 1.3 mg/dL)	31 (28.4)	43 (14.2)	68 (21.3)	**0.001**	0.12
Haemoglobin <120 g/L	34 (31.8)	52 (17.2)	65 (20.0)	**0.001**	**0.012**

Lymphocytes count <1000 cells/µL	51 (48.6)	112 (39.0)	45 (15.0)	0.09	**<0.001**
C-reactive protein >5 mg/dL	49 (53.8)	157 (55.1)	32 (19.0)	0.84	**<0.001**
D-dimer >500 ng/mL	60 (72.3)	150 (60.0)	19 (20.4)	**0.04**	**<0.001**

[1]*P values refer to comparison between cases and control group A*

[2]*P values refer to comparison between cases and control group B*

ACS: acute coronary syndrome; BPM: beats per minute; ED: emergency department; IQR: interquartile range; SD: standard deviation

Table 3: Magnitude of statistically significant association found in the adjusted analysis.

	Odds ratio (95% CI)
Risk factors to develop acute coronary syndrome in COVID-19 patients compared to control A (COVID-19 patients not developing acute coronary syndrome)	
Compared to baseline characteristics	
Coronary artery disease	5.86 (3.14-10.95)
Age: 60 years or older	2.34 (1.19-4.62)
Hypertension	2.15 (1.16-3.98)
Compared to clinical characteristics of the episode	
Chest pain	16.22 (8.49-31.02)
Raised troponin (>99th percentile)	4.93 (2.32-10.46)
Hypoxemia (pulse oxymetry <96%)	2.33 (1.19-4.56)
Symptoms lasting more than 3 days	0.35 (0.19-0.64)
Characteristics of acute coronary syndrome in COVID-19 patients compared to control B (acute coronary syndrome in non-COVID-19patients)	
Compared to baseline characteristics	
(none achieved statistical significance in the adjusted model)	-
Compared to clinical characteristics of the episode	
Fever (>37.3ºC)	13.70 (3.87-48.53)
Diarrhoea	6.38 (1.45-28.08)
Cough	6.09 (2.25-16.49)
Dyspnoea	2.53 (1.31-4.87)
Lymphopenia (<1000 µL/mL)	2.40 (1.20-4.79)

The number of patients presenting the baseline and current episode conditions in each group can be consulted in Table 1.